REMARKS

This Amendment cancels claims 26, 34, 44 and 47, and amends claims 20, 22, 24, 27, 28, 31, 38, 42, 45 and 48. The 2.0 wt-%/h minimum dissolution rate feature of claims 20, 24, 38 and 42 is taken from canceled claims 26 and 44. The amendments to claims 27 and 45 merely change their dependency. The remaining changes to claims 20, 22, 24, 28, 31, and 48 are merely editorial. Claims 20-25, 26-29, 31-33, 35, 38-43, 45, 46 and 48-50 are pending, although claims 22-25, 28, 31, 32, 38, 40, 42, 43 and 48 have been withdrawn from further consideration by the Patent Office.

A Request for Continued Examination is attached. Entry of this Amendment is requested.

Before addressing the rejections, it may be useful to describe the applicants' invention. The inventors have discovered a sol-gel derived SiO_2 monolith, coating or particle having a fast dissolution rate can be prepared using specified values for processing parameters of (1) pH, (2) molar ratio of water to alkoxide or inorganic silicate, and (3) molar ratio of alcohol to the alkoxide or inorganic silicate. The effect of this original recipe on the structure of the resulting sol-gel can be maintained by "freezing" the structure, by permitting it to gel spontaneously

at a specified temperature, or gelling the sol by forced drying. A SiO_2 monolith, coating or particle having a slower dissolution rate can be prepared by changing (deviating) from the specified values for the processing parameters required to produce a SiO_2 monolith, coating or particle having a very fast dissolution rate.

This Amendment overcomes the 35 U.S.C. § 112, second paragraph, rejection of claims 21, 27, 29, 33-35, 39, 46 and 47. Claims 20 and 28 (and also claims 22, 24, 31 and 48) have been amended by deleting the phrase "very fast bioresorption rate", thereby eliminating the first ground for rejection.

The remaining grounds for the indefiniteness rejection are without merit. With respect to the second ground, the applicants are entitled to claim their invention as they see fit, as long as one of ordinary skill in the art can understand the metes and bounds of the claim. In this case, one skilled in the art would readily understand the changes recited in claims 20, 28 and 38. The Patent Office has merely objected to their location within the claim, and has not explained <u>why</u> their location in the claim is somehow unclear.

With respect to the third, fourth and fifth grounds for rejection, the broad scope of a claim does <u>not</u> make it indefinite

per se. See MPEP § 2173.04 ("Breadth of a claim is not to be equated with indefiniteness. In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971).") Thus, the Patent Office objections to the breadth of the claims as indefinite is improper.

With respect to the sixth ground for rejection, claims 20 and 28 expressly refer to "deviating the temperature for letting the sol gel spontaneously from the values defined in b)i)." These temperatures are expressly set forth in b)i):

> let to gel spontaneously at a temperature of ≤ 25 °C
> or an elevated temperature of 65 °C to 90 °C

One of ordinary skill in the art would have no difficulty in understanding what is meant by deviating from the temperature for letting the sol gel spontaneously from the values set forth in b)i).

The seventh ground for rejection is also without merit. Dependent claim 27 limits the dissolution rate to a faster rate than recited in claim 20. There is nothing indefinite about the dissolution rates recited in either of those claims.[1]

The plain language of claim 20 specifies there is no biologically active agent other than the SiO_2 itself present, while

[1]The corresponding objection to claims 34 and 47 is mooted by the cancellation of those claims.

the plain language of dependent claims 21, 29 and 39 additionally requires the presence of at least one biologically active agent. The Patent Office has not explained why one of ordinary skill in the art would not understand the metes and bounds of these claims.

The last objection to claims 20 and 28 is also without merit. One of ordinary skill in the art would understand these claims require correlating the parameters for preparing a sol-gel derived SiO_2 based on the biodegradability he desires the SiO_2 to possess.

Reconsideration and withdrawal of the indefiniteness rejection of claims 21, 27, 33-35, 39, 46 and 47 are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 21, 27, 29, 33-35, 39, 46 and 47 over the Kortesuo Dissertation (2001) in view of Kortesuo et al., 76 J. Controlled Release 227 (2001) is traversed. The claimed bioresorbable sol-gel derived SiO_2 has either a very fast dissolution rate (at least 2.0 wt-%/hour) or a slow dissolution rate (0.001 to 0.05 wt-%/hour). The inventors have discovered a very fast *in vitro* dissolution rate can be achieved by using a combination of specified precursor ratios (e.g., a water to alkoxide ratio of 0.5 to 2.5, and alcohol to alkoxide ratio of at least 0.5), and an initial sol pH of 0.05 to 2.5. A slower

dissolution rate can be achieved by departing from these specified sol-gel processing parameters.

The cited combination of references fails to raise a *prima facie* case of obviousness against the claimed sol-gel derived SiO_2. Neither the Kortesuo Dissertation nor Kortesuo et al. disclose or suggest a sol-gel derived SiO_2 monolith having an *in vitro* dissolution rate of at least 2.0 wt-%/hour, or the combination of precursor ratios, pH and drying conditions necessary to achieve such an unexpectedly fast dissolving SiO_2 monolith. The following points are made in response to the arguments contained in the Official Action:

1. Routine Optimization - The Patent Office argues that the claimed sol-gel derived SiO_2 could be obtained by routine optimization of the sol-gel process disclosed in the Kortesuo Dissertation. This simply is not true. The Kortesuo Dissertation's disclosure would not produce a sol-gel derived SiO_2 having a dissolution rate covered by the claims.

Table 2 on page 28 of the Kortesuo Dissertation lists various sol-gel derived SiO_2 monoliths and microparticles which were prepared using various precursor ratios, pH and drying conditions.

None of them had an *in vitro* dissolution rate of at least 2.0 wt-%/hour.

The Kortesuo Dissertation suggests the degradation rate of the silica xerogel can be "modified" by varying the composition of the starting materials, or by varying the manufacturing method from casting to spray drying. Such a statement is merely an invitation to experiment, rather than guidance to one of ordinary skill in the art seeking to prepare a sol-gel derived SiO_2 having a very fast dissolution rate.

The Kortesuo Dissertation demonstrates the prior art did not understand which factors are decisive to control the dissolution rate of bioresorbable sol-gel derived SiO_2, and how those factors can be managed without detrimentally affecting other properties of the SiO_2 important for many, if not most, applications of bioresorbable sol-gel derived SiO_2. The Kortesuo Dissertation provides only a very limited possibility of adjusting the dissolution rate of the silica gel of a monolith. In Table 2 (page 28) the dissolution rates obtained using a rather broad pH range of 1-5 resulted in a very narrow degradation rate range of 16.9 to 25.7 %/30 h (0.56 to 0.85 wt-%/h). The degradation rate range for microparticles is broader, but is still limited to 0.02 to 0.56 wt-%/h.

Similarly, the Kortesuo Dissertation provides only a very limited possibility of adjusting the dissolution rate by adjusting the molar ratio of water to alkoxide. In Table 2, a water to alkoxide ratio range of 6 to 28 resulted in a very narrow degradation rate range of 16.9 to 20.4%/30 h (0.56 to 0.68 wt-%/h). The degradation rate for microparticles is broader, but even here the degradation rate is limited to 0.01 to 0.67 wt-%/h despite using a broader alkoxide ratio range of 6 to 35.

The Kortesuo Dissertation teaches the porosity/surface area and geometry of the sol-gel derived SiO_2 affects its degradation rate. See page 31 ("In general, the porous structure of cast silica xerogel monoliths resulted in a faster...degradation of the matrix as compared to spray-dried particles.") Yet, other factors are often more decisive. See Fig. 2 of Viitala et al., "Adjustably Bioresorbable Sol-Gel Derived SiO_2 for Release of Large Biologically Active Molecules", 36 J. Sol-Gel Sci. & Tech. 147 (2005) which shows that despite a much smaller specific surface area (3.4), the degradation rate of monolith Bm12 is clearly faster than that of monoliths Bm11 (ssa of 43), Am03 (ssa of 637) and AM01 (ssa of 697).

In short, the Kortesuo Dissertation fails to disclose or suggest a starting point for correlating the values necessary to produce a sol-gel derived SiO_2 having a specific dissolution rate, as demonstrated by the results listed in its Table 2. In stark contrast, the present application provides such a starting point. The application defines what changes result in slower dissolution rates, and defines the provisos related to having these changes reduce the dissolution rate. See pages 18 to 22 of the application.

2. Specific Starting Point and Processing Parameters

The Patent Office incorrectly argues that the specific starting point and parameters for specific dissolution rates are not recited in the claims. In fact, the specific starting point is (i) the starting sol pH [0.05 to 2.5], (ii) sol molar ratio of water to the alkoxide or inorganic silicate [0.5 to 2.5] and (iii) sol molar ratio of alcohol to the alkoxide or inorganic silicate [$\geq$ 0.5] and specified gelling conditions required to produce a sol-gel derived SiO_2 having a fast dissolution rate. The claims also define which changes [changes b)1), 2) and 3) referred to in the claims] to these starting parameters should be made to produce a sol-gel derived SiO_2 having a slower dissolution rate. Now that

the applicants have identified the required starting point, one of ordinary skill in the art can easily correlate individual changes to changes in dissolution rate and determine the changes required to obtain a sol-gel derived SiO_2 having a desired dissolution rate.

The present invention offers those of ordinary skill in the art great versatility in the production of a bioresorbable sol-gel derived SiO_2, i.e., the ability to obtain a desired *in vitro*[2] dissolution rate over a great dissolution range and with certainty. These advantages were unforeseen from the Kortesuo Dissertation and the other prior art of record.

3. Degradation Times -The Patent Office argument that the Kortesuo Dissertation teaches monolith degradation times as long as 4 months (Official Action, page 3, last incomplete paragraph) is incorrect because the cited disclosure (page 35, 6.1.3) relates to alkyl-substituted monoliths (25 mol% substitution with DMDES). In contrast, the claimed sol-gel derived SiO_2 has no such substitution. See the definition of *sol-gel derived SiO_2* on page 11, lines 13 to 24, of the application. The Kortesuo Declaration

[2]The *in vitro* dissolution rate corresponds to an about 10-fold *in vivo* dissolution rate. Accordingly, the *in vivo* dissolution rate range achieved by the present invention is even greater than its *in vitro* dissolution rate range.

fails to disclose the claimed sol-gel SiO_2 having a dissolution rate of 0.001 to 0.05 wt-%/h.

4. *In Vivo* Dissolution Time - Page 4, lines 1-2 of the Official Action cites the Kortesuo Declaration for the proposition that *in vivo* dissolution times may be ten-fold slower than *in vitro* dissolution rates. However, *in vivo* dissolution rates are irrelevant to the *in vitro* SiO_2 dissolution rates recited in the claims. The claims expressly define SiO_2 dissolution rate in a TRIS buffer at a temperature of +37 C and pH of 7.4.

The secondary reference does not provide any additional information which would permit one of ordinary skill in the art to arrive at the claimed invention. The Patent Office concedes that Kortesuo et al, 2001 does not explicitly exemplify the instantly claimed monoliths (Official Action, page 4, lines 16-17).

Reconsideration and withdrawal of the obviousness rejection of claims 21, 27, 29, 33-35, 39, 46 an 47 are respectfully requested.

The provisional obvious-type double patenting rejection of claims 21, 27, 29, 33-35, 39, 46 and 47 over claims 24, 25 and 30-33 of co-pending, commonly-assigned U.S. patent application S.N. 09/913,643 in view of Kortesuo et al., 76 J. Controlled Release 227 (2001) is again noted. Contrary to the statement in the Official

Action, the '643 application claims do not *anticipate* any of the claims in this application. The '643 application claims are directed to a fiber, a delivery device comprising the fiber and a method for administering a biologically active agent to a human or animal which comprises implanting, injecting or mucosally attaching the device. In contrast, the claims of this application are directed to a monolith, particle or coating.

As demonstrated above, the claims of this application are otherwise in condition for allowance. The Examiner is requested to withdraw this provisional non-statutory to permit this application to issue. A corresponding non-provisional obvious-type double patenting rejection can be entered by the Board in the '643 application upon issuance of this application.

The RCE filing fee is being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is

authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

James C. Lydon
Reg. No. 30,082

Atty. Case No.: **TUR-186**
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

Enclosure:
Request for Continued Examination